

### REMARKS

Claims 57-75, 87-92, and 99 are currently pending, claims 76-86, 93-98, and 100 having been cancelled without prejudice. The amendments to claim 57 remove "non-neural tissue or bodily fluid" or merely rearrange or restate elements already present in the claim; in addition, these amendments are supported by the specification, pre-amendment claims 57-100, and original claims 1-56. The amendments to claims 72-74 and 89-91 remove "bodily fluid" or "bodily fluid of the individual is" and add "cells are cells within a sample of"; the latter is supported by the specification, and by, for example, claims 57 and 87. The amendments to claims 75 and 92 remove "non-neural tissue is mucosal tissue" and add "cells are cells within a sample of cheek scrapings"; the latter is supported by the specification, as well as by, for example, original claims 13 and 14. The amendments to claim 87 merely rearranges or restates elements already present in the claim; in addition, these amendments are supported by the specification, as well as by pre-amendment claims 57 and 87. This amendment adds no new matter.

The invention includes, but is not restricted to, methods for creating a gene profile for a given stage of Alzheimer's disease, methods for determining whether an individual has Alzheimer's disease, and methods for determining whether a compound affects the gene profile for a given stage of Alzheimer's disease.

### Specification

Applicants have amended the specification to remove the browser-executable code at page 25.

### Priority

The Examiner states that "[t]he filing date of the instant claims is deemed to be the filing date of the present application, 01/25/2001" (Office Action at page 2). Solely for the purpose of advancing prosecution Applicants have amended the claims so they no longer include subject matter the Examiner found to be new matter. However, Applicants do not agree that the subject matter removed in this amendment is indeed new matter, and they wish the record to reflect that they have made this amendment without prejudice. Furthermore, Applicants wish to clarify that

the priority date for all claims pending prior or subsequent to the current amendment is that of United States Provisional Patent Application Serial No. 60/063,274, filed on October 24, 1997. Applicants note that the priority date bears on the current rejections for lack of novelty and for obviousness.

35 U.S.C. §102

Claims 57-59 were rejected as allegedly being anticipated by Allen *et al.* (*Neuroscience Lett.* 132:109-112, 1991; herein, "Allen"). The Examiner states that Allen "teach a method for creating a gene profile for a given stage of Alzheimer's disease" (Office action at page 3).

In view of the present amendment, this ground for rejection should be withdrawn. The test for anticipation is identity; to anticipate, a single prior art reference must disclose each and every element claimed, either explicitly or inherently (MPEP 2131). Neither Allen nor any of the other allegedly anticipatory prior art references cited in the Office Action meet this test.

More specifically, Allen examined only the expression of  $\beta$ -amyloid precursor protein ( $\beta$ APP) mRNA peripheral mononuclear blood cells (PMBCs) obtained from patients believed to have Alzheimer's disease. Allen's teaching is strictly limited to analysis of  $\beta$ APP mRNA.

By contrast, Applicants' claimed method requires "determining the level of expression of the mRNAs of more than one gene in the population of mRNAs" (claim 57; emphasis added). There is no suggestion in Allen that one should determine the level of expression of the mRNAs of any gene other than  $\beta$ APP, nor is there any suggestion that one should determine the level of expression of mRNAs of multiple genes in a heterologous population of mRNAs. Applicants note that claims 58 and 59 depend from claim 57, and that, as Allen does not anticipate amended claim 57, it cannot anticipate claims 58 or 59.

Applicants have made the present amendment for the sole purpose of advancing prosecution. This is not an admission that Allen anticipates any of claims 57-59 as originally filed, and Applicants expressly retain their right to prosecute these original claims without prejudice.

Claims 57-59, 65, 73, 87, 88, 90, and 99 were rejected as allegedly being anticipated by Markham *et al.* (U.S. Patent No. 5,952,481; herein, "Markham"). The Examiner states that

“Markham *et al.* teach creating a gene profile for a given stage of Alzheimer's disease (Col. 24), providing a plurality of cells from non-neural tissue or bodily fluid of a patient who has Alzheimer's disease (Col. 24 lines 33-38)” (Office Action at page 3). Applicants respectfully request reconsideration.

With respect to diagnosis, Markham stated, “[t]he identification of *mutations* in the class of human HUBC4 genes would aid in diagnosis” (at 6:49-54; emphasis added). Diagnostic methods are also described at 12:5-10, but these methods rely on comparison “of test DNA sequence structure from an individual to be tested with the sequence structure shown in FIGS. 1, 2, or 14, or parts thereof.” Thus, Markham is looking for *mutations*. *See also* 12:43-48. Markham's absolute focus on mutations is evident in the Example at columns 23-24 as well. Markham states, “[I]n this way any mutations occurring in the HUBC4 mRNA in the individual under investigation will be detected” (Col. 24, lines 47-49; emphasis added).

The methods claimed by the Applicants are quite different from those disclosed in Markham. As noted above, Applicants claim methods for creating a gene profile for a given stage of Alzheimer's disease (claim 57 and its dependencies), related methods for diagnosing Alzheimer's disease using such gene profiles (claim 87 and its dependencies), and methods for identifying compounds capable of altering these gene profiles (claim 99 and its dependencies). Nowhere does Markham disclose such methods; nowhere does Markham suggest determining the level of expression of mRNAs in a population of mRNAs. Instead, Markham discloses distinctly different methods that center on detecting particular mutations in genes in the HUBC gene family.

Accordingly, Applicants respectfully request the withdrawal of this ground for rejection.

Claims 57-59, 65, 73-75, 87, 88, 90, 91, 92, and 99 were rejected as allegedly being anticipated by Au-Young *et al.* (U.S. Patent No. 6,500,938; herein, “Au-Young”). This ground for rejection should be withdrawn because Au-Young is not prior art. Applicants are entitled to claim the benefit of the filing date of U.S. Provisional Patent Application Serial No. 60/063,274 because this application discloses all of the claimed elements of claims 57-59, 65, 73-75, 87, 88, 90, 91, 92, and 99 (as well as the rest of the pending claims). For example, independent claim 57 is supported by original claim 1 at page 65 in the priority Provisional Patent Application. Au-Young was filed on January 30, 1998. Since this date is subsequent to Applicants' priority date

of October 24, 1997, Au-Young is not prior art and cannot be applied in any manner against the present application.

Accordingly, Applicants respectfully request the withdrawal of this ground for rejection.

35 U.S.C. §103

Claims 60-62 were rejected as allegedly being obvious over Allen in view of Ikeda *et al.* (*Human Pathology* 21:1221-1226, 1990; herein, "Ikeda") (Office Action at pages 6-7).

Applicants respectfully request reconsideration. While the test for anticipation (the prior disclosure of subject matter that is identical to that now claimed) is different from the test for obviousness, a *prima facie* showing of obviousness requires that the prior art teach or suggest all the elements of the claim (MPEP 2142 and 2143). As explained above, Allen fails to disclose all of the elements of claim 57, from which claims 60-62 depend. Thus, Allen cannot, even in view of Ikeda, render claims 60-62 obvious. These references, either alone or taken together, fail to teach or suggest the elements of claims 60-62. On this ground alone, the rejection should be withdrawn.

Claims 60-62 were rejected as allegedly being obvious over Au-Young *et al.* in view of Mercken *et al.* (U.S. Patent No. 6,238,892; herein, "Mercken") (Office Action at pages 8-9). As explained above, Au-Young does not qualify as prior art, and Mercken alone cannot render claims 60-62 obvious. Mercken, alone, does not teach or suggest all of the elements of the methods claimed (indeed, had the Examiner found those elements, Applicants presume the Examiner would have found that Mercken anticipated claims 60-62, but no such rejection was made). Accordingly, this ground for rejection should be withdrawn.

Claims 63 and 64 were rejected as allegedly being obvious over Markham *et al.* in view of Callahan *et al.* (*Neurobiology of Aging* 15:381-386, 1994; herein, "Callahan") and in further view of Ghanbari *et al.* (U.S. Patent No. 5,811,310; herein, "Ghanbari") (Office Action at pages 9-12). But Markham, as noted above, does not suggest the methods presently claimed. To the contrary, Markham is limited to diagnostic methods that rely on the detection of particular mutant sequences. Markham fails completely to suggest the profiling method of Applicants' claim 57, let alone the further elements of that method required by claims 63 and 64. Moreover, neither Callahan nor Ghanbari can supply what Markham lacks. The Examiner cites Callahan

The Examiner states that "claims 57-65, 73-75, 87, 88, 90-92, and 99 are indefinite over the recitation of "non-neural tissue or bodily fluid." It is unclear from the specification what "non-neural" includes" (Office Action at page 16). For the sole purpose of advancing prosecution Applicants have amended claims 57, 75, 87, and 92 to remove reference to "non-neural". Applicants wish the record to reflect that they have made this amendment without prejudice.

Accordingly, applicants respectfully request the withdrawal of this ground for rejection.

The Examiner states that "claims 87, 88, 90-92 are indefinite...Claim 57 is a method claim, not a product claim. As a result, the method step in 87 d), of comparing an individual's and patient's profile to that profile which is created by the method of claim 57 is improper and should be amended as necessary to correct the improper dependency" (Office Action at page 17). Applicants respectfully traverse this ground for rejection. Nevertheless, solely for the purpose of advancing prosecution, Applicants have amended claim 87 to explain the method of that claim in alternative terms. Applicants wish the record to reflect that they have made this amendment without prejudice.

Accordingly, applicants respectfully request the withdrawal of this ground for rejection.

#### CONCLUSION

Applicants consider all of the pending claims to be in condition for allowance, which action they respectfully request.

because it “does teach determining the stage of Alzheimer’s by obtaining neuronal cells and exposing them to two or more antibodies” (Office Action at page 10) and Ghanbari because it “teach[es] the use of an antibody, ALZ-50, whose action is analogous to that of mAb69 and whose action is taught to be coupled with the use of the claimed MC-1 and TG3” (Office Action at page 11). Thus, Callahan and Ghanbari may teach uses of antibodies, but they do not supply the elements of claim 57 that Markham lacks. Since Markham, Callahan, and Ghanbari, even in combination, do not teach or suggest each and every claimed element of claims 57, 63 or 64 there is no *prima facie* case of obviousness. Accordingly, this ground for rejection should be withdrawn.

Claims 63 and 64 were also rejected as allegedly being obvious over Allen *et al.* in view of Callahan and in further view of Ghanbari (Office Action at pages 12-15). For the reasons noted above, Allen does not teach the elements of claim 57 (Allen is limited to examination of only one gene; it is not possible to create a “profile” from a single gene), let alone the further elements required by claims 63 and 64. This failure cannot be remedied by either Callahan or Ghanbari, which teach uses of antibodies, but do not supply the elements of claim 57 that Markham lacks. Since Allen, Callahan, and Ghanbari, even in combination, do not teach or suggest each and every claimed element of claims 57, 63 or 64 there is no *prima facie* case of obviousness. Accordingly, this ground for rejection should be withdrawn.

35 U.S.C. §112, ¶1

Claims 57-66, 73-75, 87, 88, 90-92, and 99 were rejected for allegedly lacking an adequate written description. The Examiner states that “[i]n the instantly rejected claims” the recitation of ““non-neural” stated specifically in claims 57, 75, 87, and 92 appears to represent new matter” (Office Action at page 15). Without prejudice, and for the sole purpose of advancing prosecution, Applicants have amended claims 57, 75, 87, and 92 to remove reference to “non-neural”. This ground for rejection is therefore now moot and should be withdrawn.

35 U.S.C. §112, ¶2

Claims 57-65, 73-75, 87, 88, 90-92, and 99 were rejected for allegedly being indefinite. Applicants respectfully traverse this ground for rejection.